Viral load elevation and virologic failure in children/adolescents: A practical approach

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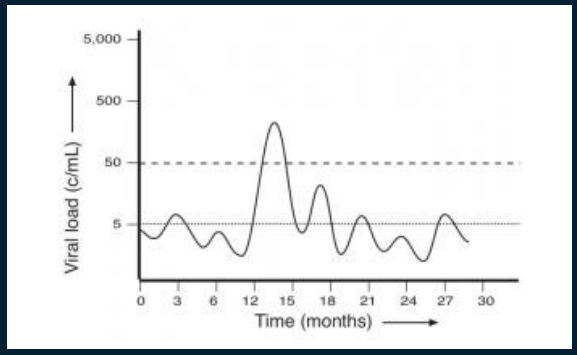
USAID
FROM THE AMERICAN PEOPLE

Background

- Viral load is the most accurate measure of treatment success
- Viral load elevation= > 50 cps/ml
- Blip= 50-<1000 cps/ml
- Virologic failure= 2X VL > 1000 cps/ml
- Virologic failure occurs in about 20% of children on ART by 3 years on treatment
- In adolescents these numbers are much higher: 50% less likely to be adherent and 70-75% less likely to have VL <400cps/ml



Patten/Fairlie, *Pediatric workshop* 2016; *IWHOD* 2017; Davies, *JAIDS* 2011; Nachega, *JAIDS* 2009

National ART regimens: 1st line

ABC and 3TC

+

LPV/rtv:
<3yr/10kg

EFV if:
>3yr+>10kg

SA National DoH combined ARV guidelines 2015

How quickly do children respond to ART?

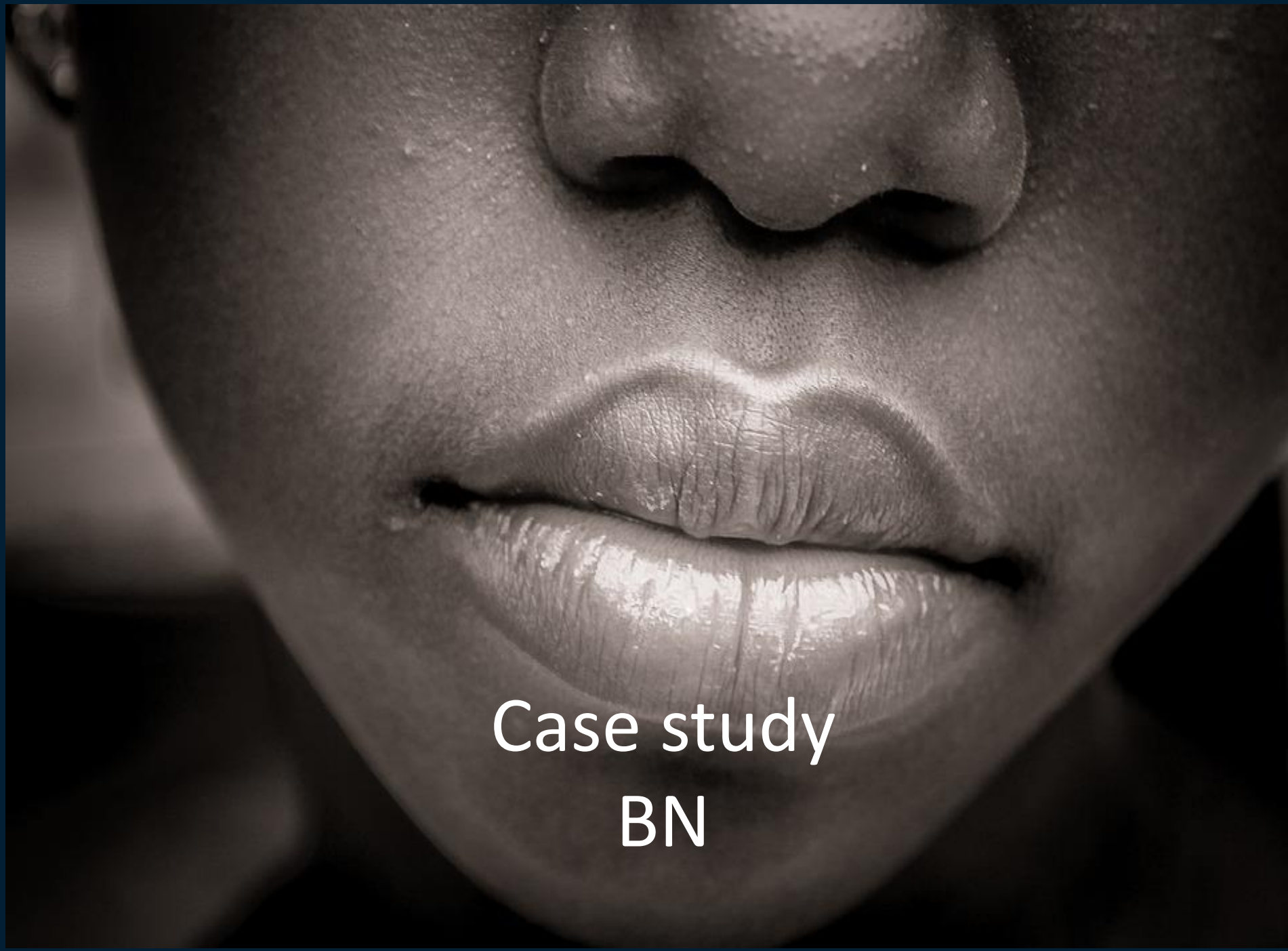
- Depends on regimen, co-treatment especially TB, adherence, absorption etc.
- Infants (median age 5.9 months)
  - 6months: 28% suppression
  - 12months: 56% suppression
- In study environments where VL are closely monitored VL suppressed as early as 12 weeks with INSTI's (eg raltegravir and dolutegravir)

Porter, *JAIDS*, 2015; Nachman, *CID*, 2014

Children are more likely to develop VF +- resistance

- Poor adherence
  - Palatability of ART
  - Pill burden
  - Formulations eg no dispersible ABC/3TC & FDCs uncommonly available
- Treatment of co-disease especially TB
- Dependency on adult
- PMTCT exposure
- Socio-economic factors

Adolescents:
- psychological and structural barriers
- peer acceptance
- disclosure
- emotional challenges of puberty


Case study
BN

History : DoB 6 Feb 2014

- Presented to Hospital with moderate respiratory distress May 2014
- Known HEU until then, received 6 weeks NVP, Maternal VL unknown
- In wards diagnosed with
  - Pulmonary TB
  - PCP
- Discharged on standard doses TB Rx, kaletra, ABC, 3TC

- Seen in ward OPD and doses not adjusted
- No super-boosting LPV/r or double dosing with TB Rx
- Eventually booked at HIV clinic February 2015…..under-dosing for 6 months
- Doses corrected but too late……

DRT

Referred for a study

	May 2015	Oct 2015	Dec 2015	Jan 2016	April 2016 (w8)	Aug 2016 (wk 24)
CD4 #	2741	2113				2165
CD4%	40.7	35.67				45.1
VL	19651	11530	201588	41014	80	<40

Subtype:

Reverse transcriptase	C (100 % similarity)	Protease	C (100 % similarity)

All Mutations Detected (HXB2 reference Sequence) Resistance mutations in bold based on **Stanford v7.0.1 (mutation score ≠ 0)**

Reverse transcriptase	P4S/T, E28K, K32E, V35T, E36A, T39E, S48T, **L74I**, **K103S**, D123N, K173A, Q174R, D177E, **M184V**, **G190A**, T200A, Q207E, L214F, **T215F**, V245Q, D250E, I257L, T286A, V292I, I293V, E297K, I329L, Q334N, G335D, **N348I**, R356K, G359A
Protease	V3I, L10M, I15V, L19T, K20R, **V32I**, E35D, M36I, S37N, R41K, **M46L**, **I47A**, K55R/wt, Q61E, L63P, C67S, H69K, V77I, L89I, I93L

Genotypic interpretation (Stanford-7.0.1)

Class	Drug	STAN 7.0.1 27/02/2014
	Zidovudine	I
	Didanosine	R
	Nevirapine	R
NNRTI	Efavirenz	R
	Etravirine	I
	Rilpivirine	I
	Indinavir/r	I
	Saquinavir/r	S
	Nelfinavir	R
PI	Fosamprenavir/r	R
	Lopinavir/r	R
	Atazanavir/r	I
	Tipranavir/r	I
	Darunavir/r	I

S
I
R

STAN
Susceptible (S) / Potential low-level resistance (PLLR)
Low-level resistance (LLR) / Intermediate resistant (IR)
High-level resistance (HLR)

Child referred for P1093, a dolutegravir study in children, doing very well

How are we doing with the 3rd 90?

Viral Suppression (<400 copies/ml), 0-19 years at 12 months
July 2015-July 2017

Source:Tier.Net

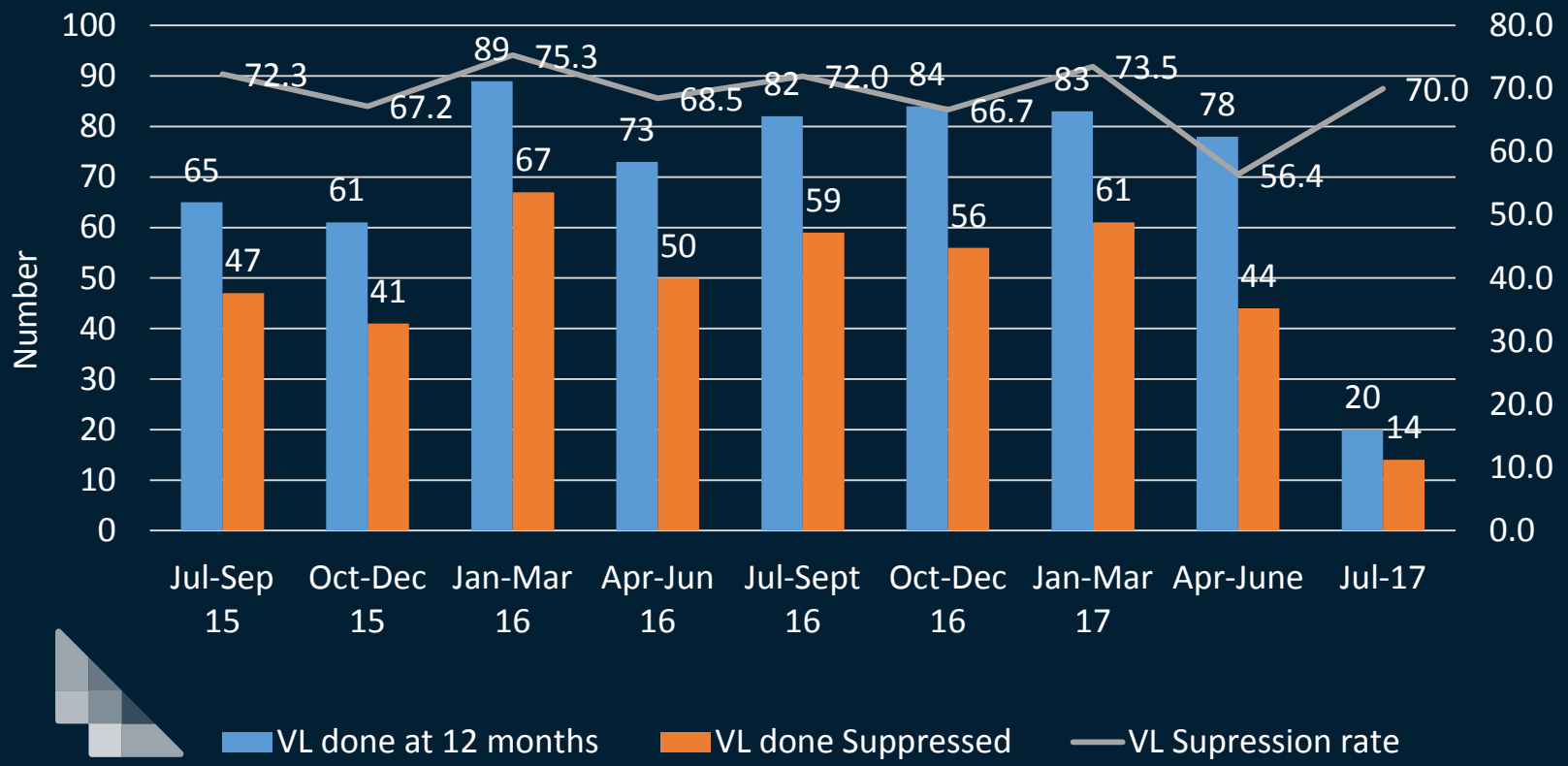
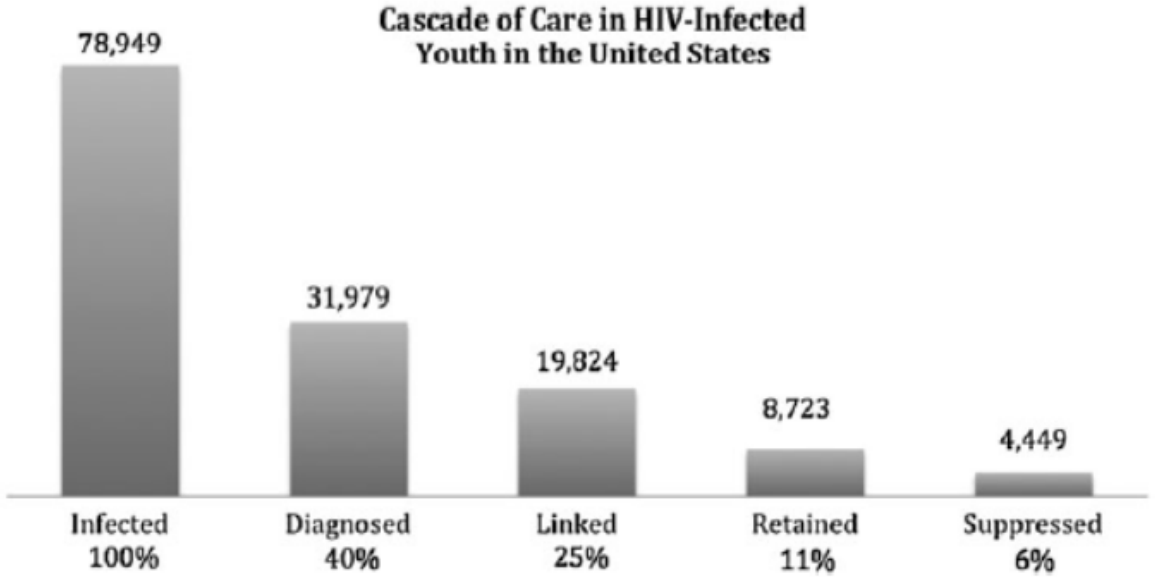
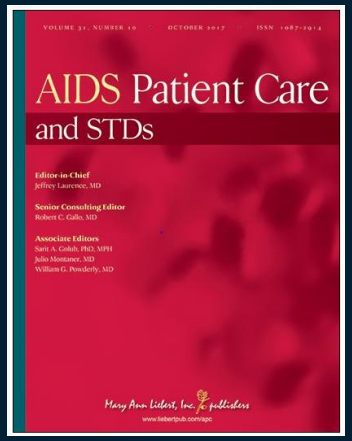


FIG. 1. Estimated cascade of care in HIV-infected youth (ages 13–29 years) in the United States.





The Adolescent and Young Adult HIV Cascade of Care in the United States: Exaggerated Health Disparities

Brian C. Zanoni, MD, MPH,[1,2] and Kenneth H. Mayer, MD[2–4]

Viral load monitoring and recommended responses

Viral load (VL)	Response
<50* copies/mL	12-monthly VL monitoring and routine adherence support
50*-1000 copies/mL	Repeat VL in 6 months Begin step-up adherence package if VL still between 50* – 1000 copies/mL
>1000 copies/mL	Begin step-up adherence package Repeat VL in 2 months If <50*, return to routine VL monitoring as above If between 50 and 1 000 copies/mL, continue step-up adherence and repeat VL after 6 months If >1 000 copies/mL, despite stepped up adherence support, AND child is on an NNRTI-based regimen, discuss with expert regarding new regimen. If >1000 copies/mL and child is on a PI-based regimen: Reinforce adherence (very difficult to fail a PI-based regimen unless the child received unboosted PI or was on rifampicin containing TB treatment while on a PI) Discuss with an expert regarding new regimen if VL >30 000 copies/mL, If the child received an unboosted PI (e.g. ritonavir alone) in the past or received TB treatment while on an LPV/r regimen and the VL is >1000 copies/mL, discuss with an expert regarding new regimen. sistance testing is indicated in these situations but should only be done if the child has been reliably :ing their ARVs in the past month.

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Second-line ART regimens for children

Second-line regimen	
Failed first-line protease inhibitor (PI) based regimen	
Failed first-line PI-based regimen	**Recommended second-line regimen**
ABC + 3TC + LPV/r	Consult with expert for advice
d4T + 3TC + LPV/r	
Unboosted PI based regimen	
Failed first-line NNRTI-based regimen (discuss with expert before changing)	**Recommended second-line regimen**
ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T + 3TC + EFV (or NVP)	AZT + ABC + LPV/r

6.4.7 Third-line ART regimens

Children who fail second-line treatment should be referred to an expert so that the treatment with third-line agents can be considered.

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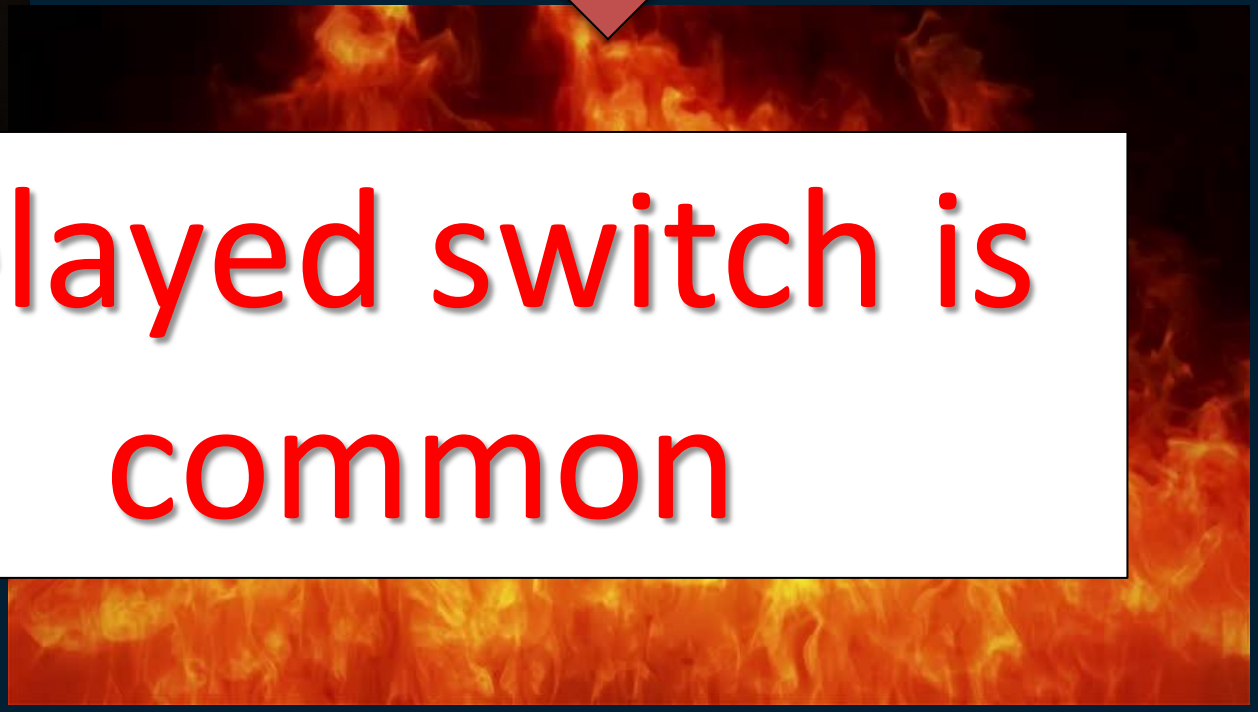
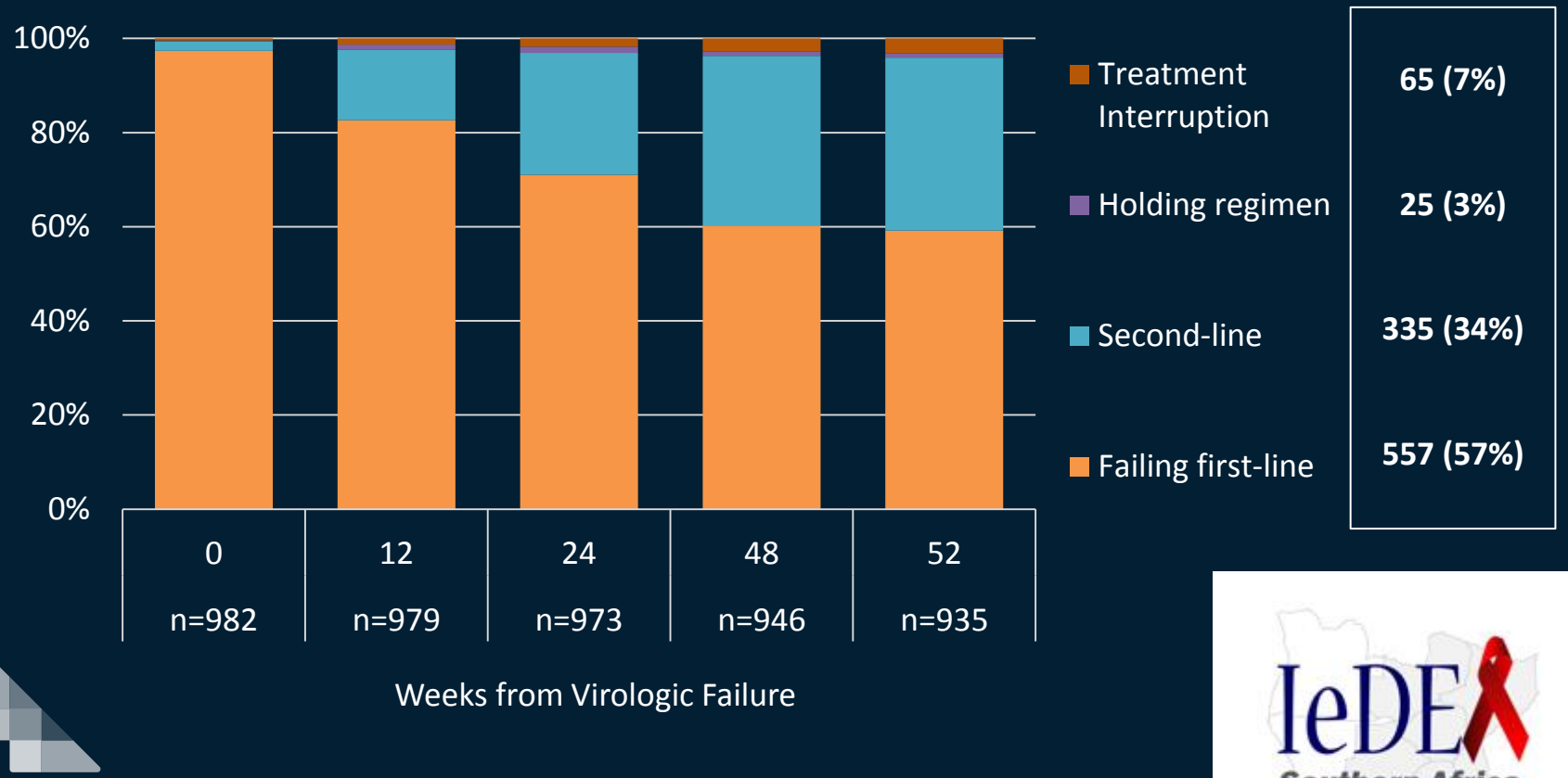
Consequences of prolonged VL elevation and VF



Delayed switch is common

Management strategies after virologic failure during study follow-up



Patten, *IWHOD*, 2017

IeDEA Southern Africa
International epidemiologic Databases to Evaluate AIDS

What happens if we don't switch?

- Many children are kept on a failing regimen
  - May need to improve adherence before switch
  - But sometimes in error
  - Do guidelines delay switch?
- Accumulation of resistance mutations particularly on an NNRTI-based regimen
- Risk of PI resistance mutations especially with previous TB co-treatment

= fewer future treatment options

Next steps

- Adherence counselling +++
- Don’t forget social determinants
- With NNRTI-based regimen switch as soon as possible
- Try to simplify regimen as much as possible eg once daily, lowest pill count, most palatable
- Need resistance testing if failing a PI
- May need to apply for a 3rd line regimen

Dolutegravir in Children
Integrase strand transfer inhibitors

- Dolutegravir has the following advantages:
  - Excellent resistance profile
  - Rapid VL suppression
  - Once daily (usually)
  - Reasonable side effect profile (but some concerns)

- Likely to be included in adult guidelines 2018
- FDA has approved 10 mg and 25 mg tablets for children > 6 years and > 30 kg
- P1093=IMPAACT study evaluating dosing and should be approved for younger ages in next few (months?) years

Conclusion

- Children and adolescents with VF and VL elevation need active management
- They have a lifetime of ART ahead of them= need as many drug options as possible
- Need to address adherence issues as successfully as possible-may be more difficult in children/adolescents
- Failure to do so has negative consequences (immediate and medium/long term)